4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers;
9) sorbitan esters;
10) polyoxyethylene sorbitan esters; and
11) calcium salts.

Marked-up version showing changes made:

1. (Amended twice) A composition of matter comprising a highly soluble salt form of sertraline having a solubility in pure water of greater than 10 mgA/ml, [or a pharmaceutically acceptable salt thereof] and an amount of a solubilizing agent sufficient to produce a concentration of dissolved sertraline in a use environment containing chloride ions which is 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent [, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.]

7. (amended once) A composition of matter as defined in claim 1, wherein said solubilizing agent is selected from the group consisting of:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers
9) sorbitan esters;
10) polyoxyethylene sorbitan esters; and
11) calcium [carbonate] salts.

10. (Amended twice) A composition of matter comprising a highly soluble salt form of sertraline having a solubility in pure water of greater than 10 mgA/ml, [or a pharmaceutically acceptable salt thereof] and an amount of a solubilizing agent sufficient to maintain, for at least 2 hours in 0.075M sodium chloride, a concentration of dissolved sertraline in a use environment containing chloride ions which is 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for

the inclusion of said solubilizing agent [, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.]

13. (amended once) A composition of matter as defined in claim 10, wherein said solubilizing agent is selected from the group consisting of:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers
9) sorbitan esters;
10) polyoxyethylene sorbitan esters; and
11) calcium [carbonate] salts.

15. (Amended twice) A composition of matter comprising a highly soluble salt form of sertraline having a solubility in pure water of greater than 10 mgA/ml [or a pharmaceutically acceptable salt thereof] and an amount of a solubilizing agent sufficient to effect, *in vivo*, a C_{max} and/or an AUC which is greater by at least 10% than the C_{max} and/or AUC effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent [, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.]

20. (Amended once) A composition of matter as defined in claim 15, wherein said solubilizing agent is selected from the group consisting of:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers
9) sorbitan esters;
10) polyoxyethylene sorbitan esters; and

11) calcium [carbonate] salts.

22. (Amended twice) A method of increasing the solubility of sertraline in an aqueous chloride ion-containing use environment, comprising administering said sertraline to said use environment in a composition of matter additionally comprising a solubilizing agent, wherein said sertraline is in the form of a highly soluble salt form having a solubility in pure water of greater than 10 mgA/ml [, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.]

29. (Amended once) A composition of matter as defined in claim 22, wherein said solubilizing agent is selected from the group consisting of:

1) organic acids and organic acid salts;
2) partial glycerides;
3) glycerides;
4) glyceride derivatives;
5) polyethylene glycol esters;
6) polypropylene glycol esters;
7) polyhydric alcohol esters;
8) polyoxyethylene ethers
9) sorbitan esters;
10) polyoxyethylene sorbitan esters; and
11) calcium [carbonate] salts.

Remarks

This application relates to a composition comprising sertraline or a pharmaceutically acceptable salt thereof and a solubilizing agent which prevents gel formation or otherwise maintains the solubility of sertraline in a use environment containing chloride ions.

Reconsideration and reexamination of this application are respectfully requested in view of the present amendments and comments. After the present amendments, the claims in this case number 1 through 67. Claims 1 through 29 are directed towards high solubility salt forms of sertraline. Claims 30 through 67 are new and are directed towards low-solubility forms combined with certain solubilizers. New claims 30 through 67 are fully supported throughout the specfication, particularly at page 5, and at pages 10 through 12. It is believed no new matter has been added by the present amendments.

The amended claims are directed toward use of a highly soluble salt form of sertraline and an excipient which acts as either a precipitation inhibitor or an antigelling agent (referred to generically as "solubilizers" in the application) to increase the amount of dissolved sertraline in a use environment. The highly soluble salt form of sertraline provides an initial enhancement of dissolved sertraline in the aqueous *in vitro* or *in vivo* use environment. The inventors herein discovered a problem, i.e. that when using highly soluble salt forms of sertraline in a use environment containing chloride ions, the dissolved sertraline quickly converted to the lower solubility hydrochloride salt form of sertraline. This could cause the viscosity of the solution to rise, resulting in the formulation of a gel, or could cause the concentration of dissolved sertraline in the use environment to decrease resulting in precipitation of a solid or gel form. The present inventors solved the problem by adding the precipitation inhibitor or antigelling agent to reduce the rate at which the highly soluble salt form gels or precipitates from solution, thus maintaining the higher concentration of dissolved sertraline for a longer period of time. The amended claims are directed toward this aspect of the invention.

The second aspect of the invention, covered in the newly added claims, is directed toward the use of low solubility forms of sertraline, such as the hydrochloride salt form of sertraline (this salt form has a low aqueous solubility). The inventors herein recognized that solubility of the hydrochloride salt form of sertraline may be improved by use of a solubilizing agent, in particular, an organic acid. The use of the organic acid solubilizer improves the concentration of dissolved sertralinc in the use environment. Once this enhanced concentration is achieved, then optionally other precipitation inhibitors or antigelling agents may be added, as described above, to maintain the high dissolved sertraline concentration.

Turning now to the Office Action, Claim 1 has been amended to require that sertraline is in the form of a highly soluble salt form having a solubility in pure of water of greater than 10 mgA/mL. Support for the amendment may be found at page 1, lines 20-23; and page 3, lines 21-23 of the patent application.

The claims have been rejected under 35 USC 102 as being anticipated by Welch, Jr. et al., U.S. 4,536,518 (hereinafter referred to as "Welch Jr. et al"). The Examiner's comments have been carefully considered and the rejection is respectfully traversed.

To constitute anticipation, all material elements of a claim must be found in one prior art source. In re Marshall, 198 USPQ 344 (CAFC 1978). Moreover, in determining whether the subject matter as a whole is obvious, all evidence bearing on the subject must be considered, In re Wiggins, 158 USPQ 199 (CCPA 1968), including all differences, whatever their nature, between the subject mattter sought to be patented and the prior art In re Krazinski et al, 146 USPQ 25 (CCPA 1965), In re Rinehart, 189 USPQ 143 (CCPA 1976).

Claim 1 clearly distinguishes over Welch Jr. et al. Claim 1 requires the combination of sertraline in the form of a highly soluble salt form and a solubilizer present in a sufficient amount to increase the dissolved sertraline concentration in a use environment. It is initially noted that there is no discussion in Welch Jr. et al.

of highly soluble salt forms of sertraline. Welch Jr. et al. describe generally a very broad class of active compounds, of which sertraline is a single species. The discussion of salt forms in Welch Jr. et al. is limited to diastereomeric salt forms used to resolve racemic mixtures (column 6, lines 17-24), and a general discussion of acid addition salts. See column 6, lines 25-34. The only forms of sertraline described by Welch Jr. et al., are the free acid and hydrogen chloride salt form. The hydrochloride salt form has a solubility of about 2.5 mg/mL. (See patent application, page 15, line 9.) Thus, contrary to the Examiner's allegations, Welch Jr. et al. do not disclose the presently claimed highly soluble salt forms of sertraline.

Additionally, Welch et al. are silent on the use of a combination of a highly soluble salt form and a solubilizers. Welch Jr. et al. list several classes of specific compounds that may be included as excipients in tablets (Col. 7, lines 22-56). However, nowhere do Welch Jr. et al., describe the particular combination of a highly soluble salt form of sertraline and a solubilizing agent in a sufficient amount to increase the concentration dissolved sertraline in a use environment. The statutory mandate of 35 USC 102 has not been met and Applicants invention cannot be said to be anticipated by the cited reference. Withdrawal of all rejections under 35 USC 102 is requested.

Claim 1 has also been rejected under 35 USC 103 as being obvious in view of Welch Jr.et al. The rejection is respectfully traversed.

Claim 1, as amended, patentably distinguishes over Welch Jr. et al. for the reasons described above. In addition,it is to be noted that the present invention lies in the recognition by the inventors herein that the solubility of sertraline was reduced in a chloride-ion containing environment. See page 5, lines 17-19 of the present specification. It was not previously recognized that a chemical agent existed that could reduce or prevent sertraline gelation. Applicants solved the problem of reduced solubility of highly soluble salts forms of sertraline in chloride-ion containing use environments by including a sufficient amount of a solubilizer. In this case, the invention lies in the discovery of the source of the problem (reduced solubility of sertraline in a chloride-ion containing use environment) and the recognition of a remedy. '[A] patentable invention may lie in the discovery of the course of a problem even though the remedy may be obvious once the source of the problem is identified; this is part of "subject matter as a whole" which should always be considered in determining ovviusness of an invention under section 103' In re Sponnoble, 160 USPQ 237 (CCPA 1969), MPEP 2141.02. Welch Jr. et al., do not disclose the invention as a wholc because Welch Jr. et al., do not recognize the problem of sertraline gelation in the presence of chloride ions nor do they teach or suggest the addition of a solubilizer to prevent or reduce gelation. Thus Claim 1 patently distinguishes over Welch Jr. et al.

Claims 7, 13, 20 and 29 have been amended to substitute calcium salts for carbonate salts. Support for the amendment may be found at page 8, lines 12-15.

New Claim 30 specifies the highly soluble salt form of sertraline. Support may be found at page 5, lines 29-30.

New Claim 31 claims preferred solubilizing agents, which are organic acids. Support may be found at page 8, lines 7-9, page 9, lines 5-9, and examples 2-4.

New claim 32 further claims mixtures of solubilizing agents, where one of the solubilizing agents is an organic acid. Support for the claim may be found at page 12, lines 1-4.

Support for the amendment that preferred solubilizing agents are organic acids may be found at page 12, lines 5-9.

New Claim 33 patentably distinguishes over Welch Jr. et al. Claim 33 requires a combination of sertraline and a sufficient amount of a solubilizing agent. The solubilizing agent is limited to organic acids having a solubility of at least 1 mg/mL in the use environment. Support may be found at page 12, lines 5-9 (organic acids are preferred) and page 10, lines 7-10 (solubilizers should have an aqueous solubility of at least 1 mg/ml). Welch Jr. et al., do not disclose the claimed combination. While Welch Jr. et al. list a variety of excipients for use with sertraline, none of these are organic acids.

Organic acids are preferred solubilizers because such compounds are capable of reacting with sertraline in a use environment containing chloride ions to form sertraline salts having a solubility greater than the hydrochloride salt form of sertraline. Thus, for example, aspartic acid may be used to form sertraline aspartate, a high solubility salt form of sertraline. Claim 33 thus distinguishes over Welch Jr. et al. because Welch Jr. et al. do not disclose the combination of sertraline and an organic acid, the organic acid being present in a sufficient amount to improve the concentration of sertraline in the use environment relation to a control composition that does not contain the organic acid.

It is respectfully submitted that the closest excipients to organic acids are alginic acid and salts of organic acids. Alginic acid is not commonly considered an organic acid by individuals skilled in the art; rather it is considerd a polysaccharide. Specifically, it is "a linear gulosyluronic polymer consisting of a mixture of β-(1-4)-D-mannosyluronic acid and α-(1-4)-L-guloyluronic acid residue." Pharmaceutical Excipients Handbook, 3rd edition, page 10. The molecular weight is typically 20,000 to 240,000. In contrast, the organic acids described in the present specification have molecular weights ranging from 60 to 400. Moreover, alginic acid is used in pharmaceutical formulations as a suspending agent, a stabilizing agent, a disintegrant, and a binder, all uses relating to its polymeric nature. It is noted that Welch Jr. et al. list alginic acid as one of several disintegrants. Although alginic acid has carboxylic acid functionality, its use to form salts of pharmaceutical bases is not typical and may not be known at all. Thus alginic acid would not be expected to act as a solubilizer in the same fashion as the claimed organic acids.

The salts of organic acids described by Welch Jr. et al. are not as preferred as organic acids because some of such salts will not solubilize sertraline at all, while others will not improve solubility as much as the corresponding organic acid. Moreover, it should be noted that some organic salts alone would not be expected to solubilize sertraline at all. For example, magnesium stearate, a lubricant described by Welch Jr. et al., is hydrophobic and does not meet the aqueous solubility requirement. Magnesium stearate is practically water insoluble having an aqueous solubility of less than 0.1 mg/ml. Similarly, calcium carbonate is also practically water insoluble, having an aqueous solubility of less than 0.1 µg/ml.

Organic acids are preferred over calcium carbonate and organic acids salts such as sodium citrate. This is because the acidic nature of organic acids allows the organic acids to react with sertraline to form salts having improved solubility relative to sertraline hydrochloride. Since organic acid salts by themselves lack acidic functionality, they would not be expected to provide as much concentration enhancement as that provided by the organic acids.

Moreover, Welch Jr. et al., is silent with respect to the problem solved by Applicants' herein, namely the solubilization of sertraline. There is no teaching or suggestion in Welch Jr. et al., that the solubility of sertraline may be enhanced by organic acids. Accordingly, Claim 33 patentably distinguishes over Welch Jr. et al.

Claims 33-61 contain the same limitations as Claim 33, and thus patentably distinguish over Welch Jr. et al., for the same reasons.

Accordingly, in view of the present amendments and comments, the rejections under 35 USC 103 have been obviated. Withdrawal of such rejections and allowance to issue are earnestly requested.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§ 1.16 and 1.17, or to credit any overpayment to Deposit Account No. 16-1445.

Respectfully submitted,

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